



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: ) Art Unit: 1615  
)  
Gilbert J. GRANT et al ) Examiner: K. Gollamudi  
)  
Appln. No.: 10/620,006 ) Washington, D.C.  
)  
Date Filed: July 16, 2003 ) Confirmation No. 7468  
)  
For: LIPOSOMAK COMPOSITIONS ) ATTY.'S DOCKET: GRANT=1A  
AND METHODS OF PREPARATION)

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner for Patents  
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Sir:

I, Yechezkel Barenholz, do hereby declare that I am one of the inventors of the above-identified application.

Experiments were conducted under my direction and control to demonstrate that it is critical when preparing liposomes according to the present invention that the liposomes be washed with hyperosmotic saline in order to reduce the liposome size and provide a higher than expected concentration of bupivacaine.

Liposomes produced by the dehydration-rehydration (DRV) technique loaded with bupivacaine were prepared and

washed with normal saline solution. The liposomes so washed had 12.90 mg bupivacaine/ml (36.0 nmol·phospholipid (PL)/ml).

The same liposomes when washed with normal saline followed by a final wash with a hyperosmotic saline, resulted in 25.9 mg bupivacaine/ml (95.5 nmol PL/ml).

The final wash of the bupivacaine-loaded liposomes partially dehydrated the liposomes, resulting in reduced liposomal size and intraliposome aqueous phase, and therefore a higher liposome pellet concentration, and an almost two-fold higher concentration of bupivacaine.

In addition, the formation of the liposomes under conditions in which the drug is at a supercritical concentration, as in the present invention, followed by partial dehydration of the liposomes with a hyperosmotic saline, resulted in the precipitation/gelation of the drug within the liposomes and thereby reduced leakage of the drug from the liposomes.

The results described above clearly demonstrate that a higher concentration of bupivacaine is obtained when performing an additional wash of the liposomes with hyperosmotic saline.

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and

further that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 81 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By

  
\_\_\_\_\_  
Yechiel BARENHOLZ

Date: 24, August, 2004

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## Local Anesthetics

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**Gum Disease****Treatment of Perio****Prevention****Partial Dentures****Root Canals****Post and Core****Extractions****TMJ****Orthodontics****Crowns****Dental Implants****Snore Guards****Deprogrammer****Fluoride****Cracked Teeth****Aids****Dental Materials****Oral Anatomy**

It is estimated that the average dentist administers between 1500 and 2000 injections of local anesthesia each year. By definition, every dentist is an expert in the field of local anesthesia, which is an extremely good thing, since without the ability to produce profound numbness, modern dentistry would be all but impossible.



## The history of local anesthetic agents.

Surprisingly, the first local anesthetic was Cocaine which was isolated from coca leaves by Albert Niemann in Germany in the 1860s. The first clinical use of Cocaine was in 1884 by (of all people) Sigmund Freud who used it to wean a patient from morphine addiction. It was his colleague Karl Kollar who first noticed its anesthetic effect. In 1884, Dr. William Stewart Halsted was the first to describe the use of cocaine into a sensory nerve trunk to create surgical anesthesia. Halsted was an eminent surgeon who had been trained in Britain and was the first to establish formal surgical training for physicians in America. Prior to that time, surgery was a self taught discipline among US physicians. He also invented and pioneered the use of rubber gloves. Unfortunately, much to his own regret, he began to use cocaine himself and became highly addicted to it. At that time, there was no stigma attached to the recreational use of cocaine, and it gained a following among the elites of the day. Arthur Conan Doyle's Sherlock Holmes was supposed to be an addict, and Holmes kept Dr Watson around as a source for his drugs, as well as for the comic relief he provided.

It became fairly obvious fairly quickly that while the anesthetic characteristics of cocaine were desirable, the euphoria and subsequent addiction it produced was not! The turn of the century was a time of scientific progress, and the new discipline of organic chemistry enabled the synthesis of the first analog of cocaine in 1905. (An analog of a chemical molecule is one in which the original molecule is

**Understanding Pain**

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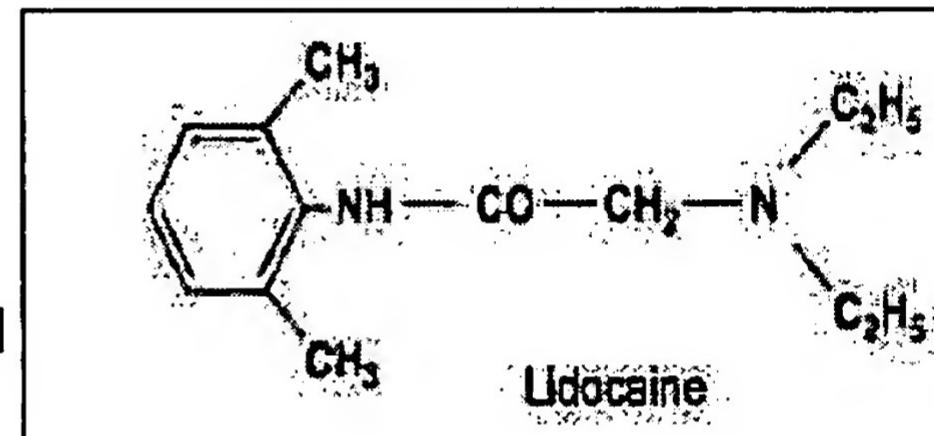
progressively modified to retain and enhance certain holistic characteristics of the original substance while ridding it of other characteristics.) The first synthetic local anesthetic was **procain** remembered today by its trade name, "**Novocain**".

Novocain was not without its problems. It took a very long time (ie. to produce the desired anesthetic result), wore off too quickly was not nearly as potent as cocaine. On top of that, it is classified ester. Esters tend to have a very high potential to cause allergic reactions. It is estimated that about one third of all persons who received it developed at least minor allergic reactions to it. Face the legal and ethical difficulties associated with the use of cocaine local anesthetic, and with the inefficiencies and allergenicity associated with the use of procaine, it is not surprising that most dentists of worked without any local anesthetic at all. (Nitrous oxide gas was available during this period.) Today, procaine is not even available for dental procedures.

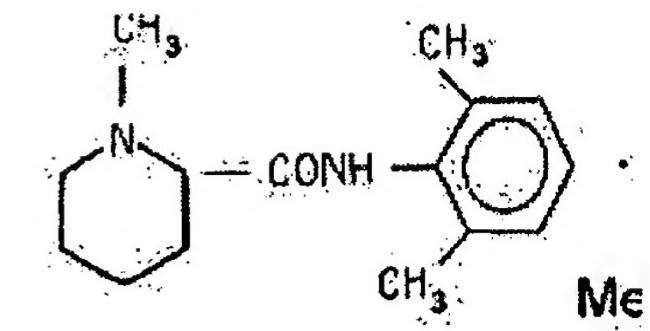
The first modern local anesthetic agent was **lidocaine** (trade name **Xylocaine®**). It was invented in the 1940s. Prior to its introduction, Nitrous oxide gas (plus alcohol in the form of whiskey) was the major source of pain during dental procedures. Lidocaine proved to be so successful that during the 1940s and 1950s the use of Nitrous oxide gas as a primary anesthetic agent all but vanished. (Whiskey somehow survived, no longer used on patients.) Today, nitrous oxide is used principally as an anti-anxiety palliative. Lidocaine is in a broad class of chemical amides, and unlike ester based anesthetics, amides tend to be hypoallergenic. It sets quickly and when combined with a small amount of **epinephrine (adrenalin)**, it produces profound anesthesia for hours. Lidocaine is still the most widely used local anesthetic in use today.

Over the next thirty years, a number of other amide local anesthetics were invented, most not differing significantly from lidocaine. The problem with lidocaine and its analogs is that they cause **vasodilation** (the tendency of the local blood vessels to open wider increasing blood flow in the area). This causes the anesthetic to be absorbed too quickly to take effect. Hence these anesthetics are always mixed with low concentrations of epinephrine which has the opposite effect (ie **vasoconstriction**) and closes the blood vessels down to keep the anesthesia in position long enough to produce long lasting numbness.

**Mepivacaine (Carbocaine®) and**



**pilocaine (Citanest®)** have much less vasodilative qualities and hence can be used without the epinephrine vasoconstrictor. The advantage to this is that these anesthetics can be used more safely in patients who are taking medications which may interact negatively with the vasoconstrictor. These drugs include certain blood pressure medications (most notably beta blockers and MAO inhibitors), tricyclic antidepressants (Elevil® and imipramine are two examples) and thyroid replacement hormones (Synthroid®).

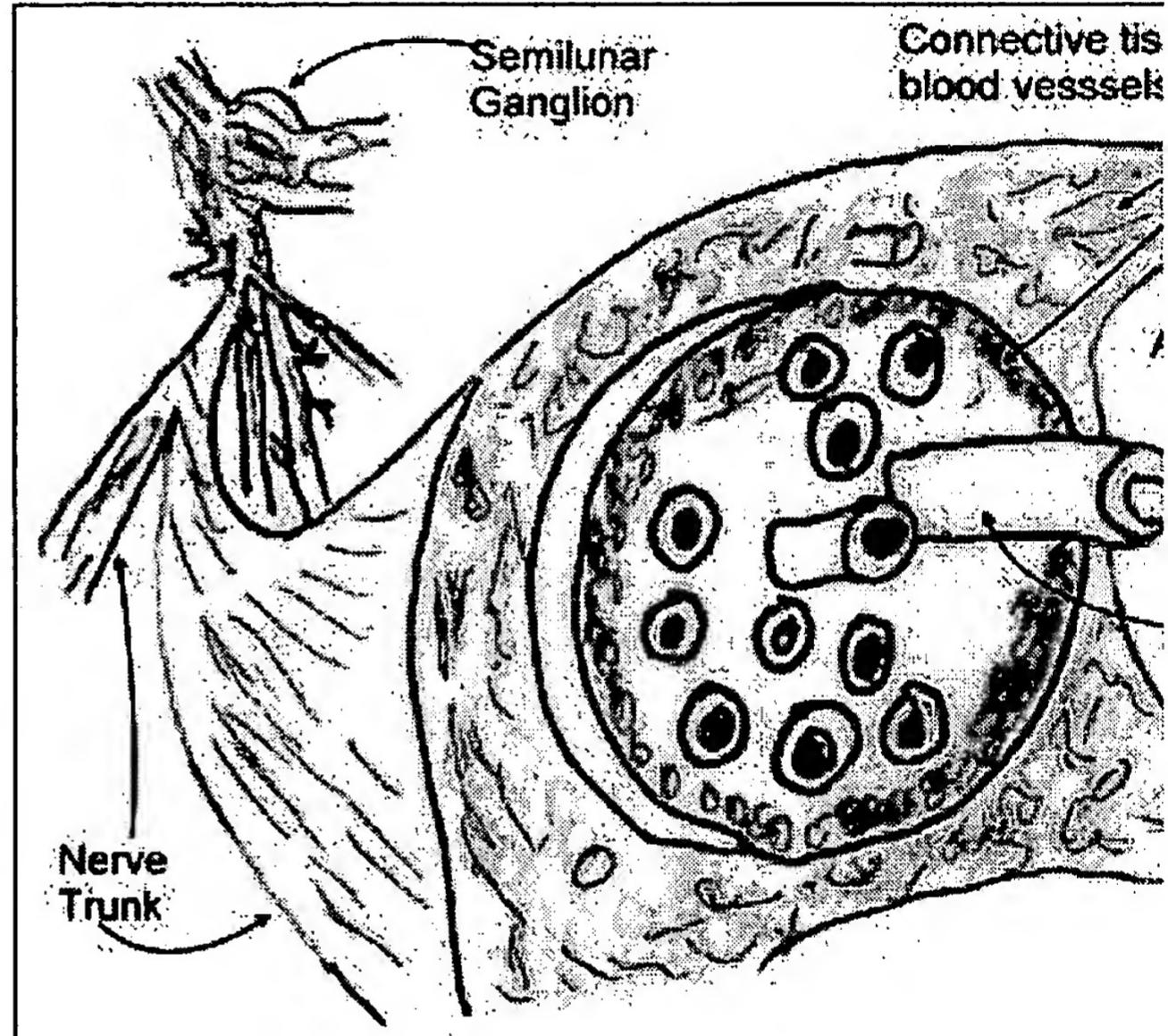


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## How nerves conduct an impulse

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The image to the right is a fairly accurate representation of a nerve bundle. (For a detailed explanation of this diagram as well as nerve anatomy and physiology, see my page on [Understanding Pain](#).) If you think of a nerve bundle as an electrical cable, the blue axons represent the



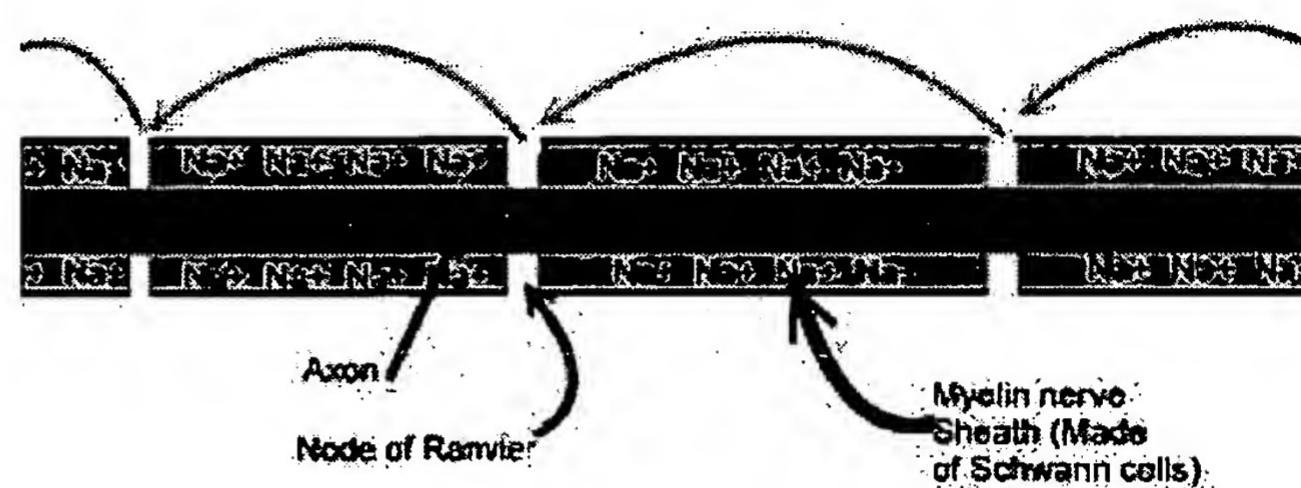
"wires" that carry the impulse from the tooth to the ganglion at one end. The rest of the tissue surrounding the axons represent the "insulation" which separates the various wires in the cable from each other. At this point, the analogy breaks down because, while the insulation in an electrical cable is a passive material that serves to separate the wires from each other to prevent short circuits, the insulation in a nerve bundle is an active participant in the conduction of the impulse.

The connective tissue that is associated with each neuron is composed of a special material called **myelin** which is itself made up of the cells of specialized cells called **Schwann cells**.

The myelin sheath is almost continuous along the entire axon. There are, however tiny breaks in the continuity of the myelin sheath at each succeeding Schwann cell. These breaks are called "**nodes**

**Ranvier".** These nodes are quite important in the conduction of impulse along a nerve axon on its way to the cell body in the ganglion mostly because their presence along the way speeds the impulse a bit.

### How a nerve fiber transmits an impulse



Nerves are NOT like electrical wires with electrons traveling through them to transfer information from one end to the other. They are actually complex electro-chemical structures which utilize the electrical potential difference between the fluid inside of the axon, and the fluid that surrounds the axon. The fluid inside the axon (called cytoplasm) has a high concentration of potassium ions, while the fluid outside contains a high concentration of sodium ions. There is no real difference in potential between a potassium ion and a sodium ion, however, the fact that they exist in different concentrations on either side of the cell membrane sets up an electrochemical pressure gradient between the two. Sodium ions want to flow into the nerve cytoplasm, while the potassium ions want to flow out, but both are prevented from doing so by the presence of the nerve cell membrane.

When a nerve is stimulated, this sets up a chain reaction in which sodium ions begin to penetrate through the nerve cell membrane and flow into the axon, while potassium ions begin to flow out. This activity happens at the nodes of Ranvier. This process is called **depolarization** of the nerve membrane. The imbalance in the chemical makeup of the extracellular fluid then causes an imbalance in the concentration of sodium ions at the adjacent node which stimulates an identical depolarization at this node as well. This process proceeds from node to node until the impulse reaches the cell body of the nerve in the ganglion where it stimulates a similar cascade in a network of other neurons which make contact with it.

You might think that once all the potassium and sodium ions have exchanged places, the nerve would no longer be able

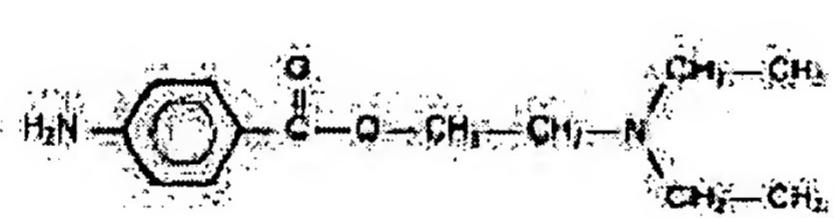
to conduct impulses. The nerve, however, is a living entity and can regenerate the original concentrations of ions using energy from the food you eat in almost the same way that muscle cells use that same energy to cause muscle movement. It does this using proteins embedded in the cell membrane which act as "ion pumps".

### How local anesthesia interrupts this process

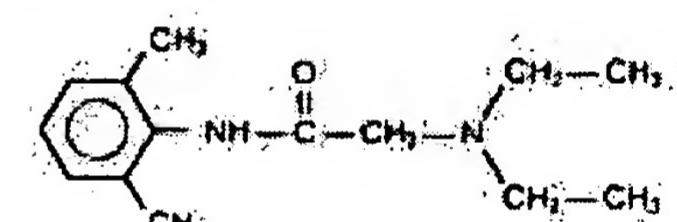
Local anesthetics work to block nerve conduction by reducing the influx of sodium ions into the nerve cytoplasm. If the sodium ions cannot flow into the neuron, then the potassium ions cannot flow out, thus inhibiting the depolarization of the nerve. If this process can be inhibited for just a few nodes of Ranvier along the way, then nerve impulses generated downstream from blocked nodes cannot propagate to the ganglion. **In order to accomplish this feat, the anesthetic molecules must actuate through the cell membrane of the nerve. Herein lies the differences in the potency, time of onset and duration of the various local anesthetics.**

### The structure of local anesthetics

Amino-esters



Amino-amides

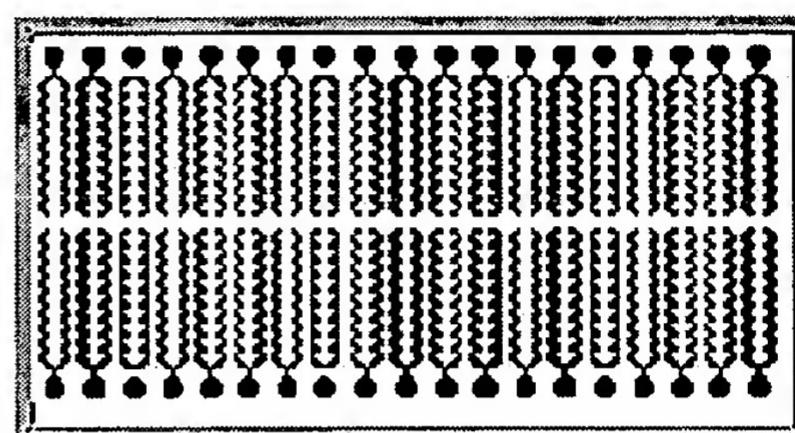


The diagrams above show the essential structures of the two major classes of local anesthetic agent; the molecule shown in the left diagram represents the structure of procaine (Novocain). The chain that connects the benzene ring on the left with the amide tail on the right is an "ester linkage". The diagram to the right represents lidocaine and its a lidocaine. The connecting chain in this case is called an "amide linkage". The amide linkage contains an extra nitrogen to the left of the C=O (carboxyl) group.

All local anesthetics are weak bases. They all contain: 1. an aromatic group (the benzene ring seen on the left side of both structures); 2. an intermediate chain, either an ester or an amide; and 3. an amino group seen on the right side of both molecular structures above. The characteristics of any given anesthetic is determined by the exact structure and relationship of each of these three components. The aromatic ring structure is soluble in lipids (The nerve cell membrane is made of a lipid bilayer and thus the aromatic ring is important in making it possible for the anesthetic molecule to penetrate through the membrane).

membrane. The amino structure (seen on the right side of the diagrammed above) is soluble in water which is what makes it possible for the anesthetic molecule to dissolve in the water in which it is delivered from the dentist's syringe into the patient's tissue. It is also responsible for allowing it to remain in solution on either side of the nerve membrane. The trick that the anesthetic molecule must play is crossing from one side of the membrane to the other.

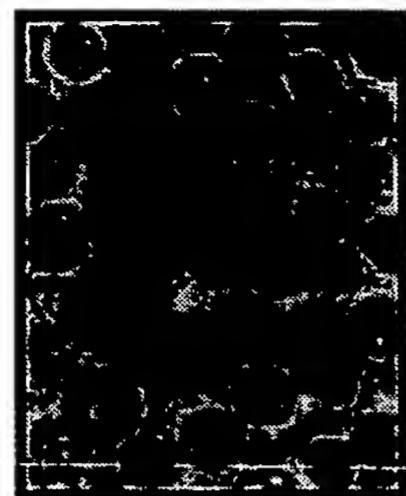
### The structure of the cell membrane



Every cell in the body has a membrane which separates that cell from other cells, and from the extracellular fluids that surround it. This membrane has a definite chemical structure which creates a stable two-dimensional sheet which naturally retains its structure in aqueous (water-based) solution. It is composed of a bilayer of phospholipid molecules arranged as shown in the diagram above. Each phospholipid molecule is composed of two components; a phosphate radical (shown as a blue oval) which tends to carry an electrical charge, and therefore likes to associate with water molecules, and two long hydrocarbon chains (green) which do not carry a charge and therefore tend to associate with each other in order to avoid contact with the surrounding water molecules. (No oil, which does not mix with water either). The stability of this sheet is based on the fact that the phosphate radicals face outward into the surrounding medium. They are soluble in water and mix well with it. On the other hand, the lipid tails are hydrophobic and avoid contact with water relying on the phosphate radicals to "protect" them. The lipid tails mingle with each other in the same way that the pioneers used to "stack the wagons" in order to protect themselves. This maintains the integrity of the membrane. This super stable micro structure is probably one of the most important chemical structures in all of creation because it enables the formation of discreet biological elements separated into cellular components.

While the phospholipid bilayer defines an essentially two dimensional sheet, it actually has a third dimension meaning that it has thickness. In addition, the bilayer is essentially a non aqueous liquid, and as such other structures such as proteins can be embedded within it, floating around in this miniature ocean of phospholipids. The proteins can have complex shapes and functions depending upon the structure pro-

for them by the genetic machinery of the cell. It is thought that channels that allow the influx of sodium ions, as well as the efflux of potassium ions during depolarization of the membrane are actually complex protein structures embedded in the neuron membrane.



The phospholipid bilayer not only exists as a chemically defined entity. It can actually be seen on electron micrographs. The thumbnail on the left shows HIV viroids budding from a natural human T cell. The lipid bilayer is clearly visible both in the mother cell and in the budding viroids. Click the thumbnail to view the image at full resolution.

## **PH, PKa, Acids and Bases---and why they are the key to the effectiveness and longevity of an injectable local anesthetic**

This section is quite conceptually difficult because it involves some essential chemistry, but it makes for very rewarding reading because it will enable the reader to understand the differences between the common local anesthetic solutions. It will help to explain the reasons that some anesthetics take longer to set than others, and why some cause more prolonged anesthesia than others.

Synthetic anesthetics are prepared as weak bases and during manufacture, precipitate as powdered solids. These solids are poorly soluble in water. They are therefore combined with an acid to form a salt which can be combined with sterile water or saline. The salt dissolves to produce a stable solution which is injectable. The PH (the acid/base balance) of the solution is adjusted to complement the specific molecular structure of the anesthesia in question. Remember that the lower the PH, the more acidic the solution is, and the higher the PH, the more alkaline (basic) it is.

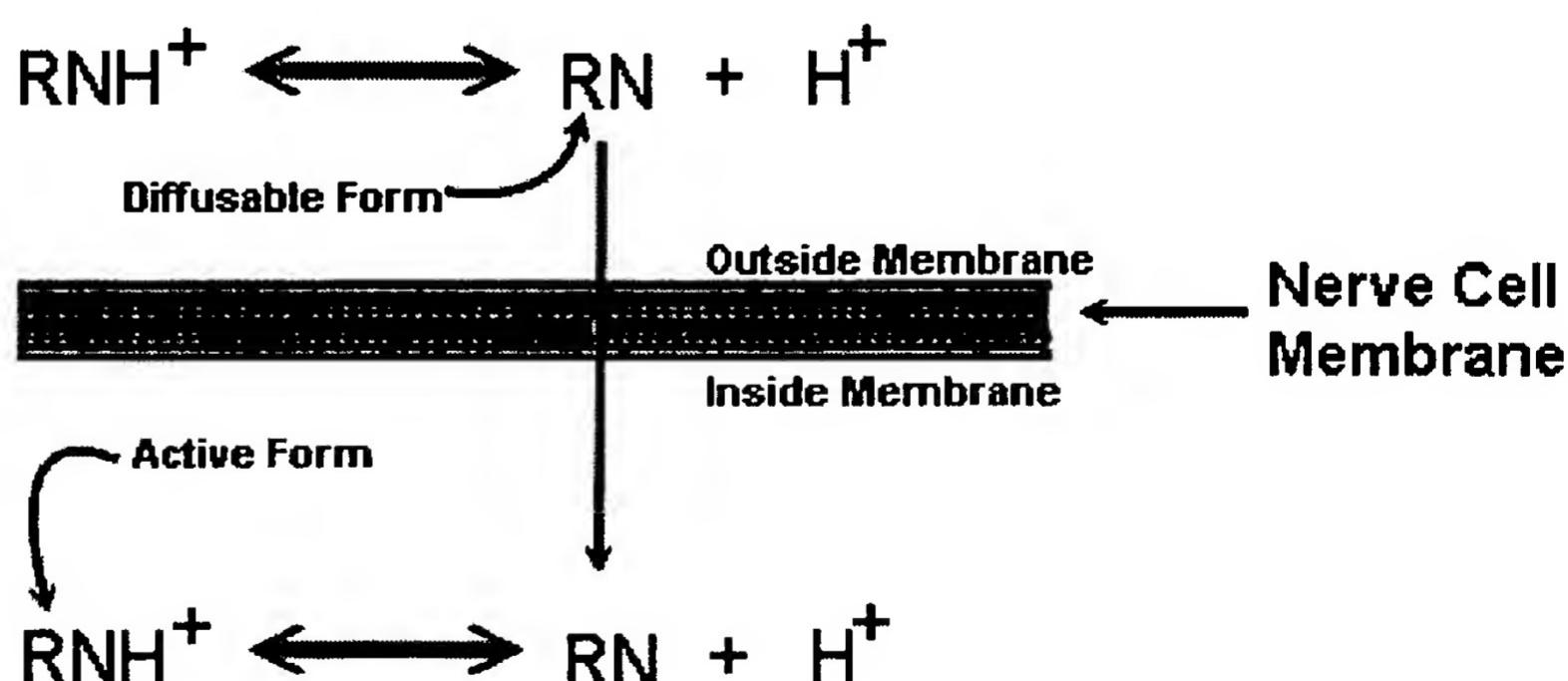
In any given solution of anesthetic, the molecular structure shifts between two forms; an uncharged base molecule ( $RN^-$ ) and a positively charged cation ( $RNH^+$ ). ("R" stands for the chemical term "radical" and is the symbol for the generic molecular structure, whether it carries a charge or not.) These two forms of the anesthetic molecule exist in an equilibrium:

equilibrium dependent upon the exact PH of the solution:



As the solution becomes more acidic (lower PH), the concentration of hydrogen ions increases. These positively charged ions combine with the uncharged anesthetic radical (molecule) shifting the above equation to the left, and producing a higher proportion of charged cationic species. As the PH rises, (ie. the solution becomes more alkaline) there are fewer positively charged hydrogen ions. Thus the charged radicals tend to release their hydrogen ions into solution and the equation shifts to the right producing more of the uncharged base.

The PH that produces an **equal** number of uncharged basic molecule (RN) and charged cationic forms (RNH<sup>+</sup>) is called the **PKa**. This is important because **the molecular form of the anesthetic that is able to diffuse through the lipid membrane of the nerve cell is the uncharged (RN) form, while once inside the neuron, the active form that inhibits sodium influx is the charged cationic (RNH<sup>+</sup>) form**. As more and more of the uncharged base diffuses through the membrane, the concentration of the uncharged base outside the membrane goes down and the formula re-equilibrates forming more of the uncharged base from the newly higher concentration of positively charged cations. This continues until all the base eventually diffuses from outside of the cell membrane to the inside. Once inside the cell membrane, the formula shifts to the left recreating the original concentrations of positive and negatively charged base molecules.



The PH of normal body tissue is 7.4. In situations in which there is an active infection present, the tissue PH can be considerably lower, in the vicinity of 5 or 6. This very reduced PH shifts the equation (outside the nerve cell) to the left reducing the number of neutral (RN) radicals available to diffuse through the nerve cell membrane. This accounts for the difficulty in anesthetizing such an area. The relative difference

between the PK<sub>a</sub> of the anesthetic and the PH of the body tissue make quite a large difference in the percentage of anesthetic available to diffuse immediately through the nerve membrane, as on the amount of time it takes for the anesthetic effect to be felt table below shows the PK<sub>a</sub> and other vital statistics of the seven commonly used dental anesthetics:

Anesthetic	PK <sub>a</sub>	% RN at PH 7.4	Onset in min.
Mepivicaine	7.6	40	2 to 5
Etidocaine	7.7	33	2 to 5
Articaine	7.8	29	2 to 5
Lidocaine	7.9	25	2 to 5
Prilocaine	7.9	25	2 to 5
Bupivacaine	8.1	18	5 to 15
Procaine	9.1	2	14 to 20

When an anesthetic solution is injected into healthy tissue, it even takes on the PH of the surrounding tissue which is 7.4. This is why the third column labeled "% RN at PH 7.4" is important. Remember that the uncharged basic RN radical can penetrate the lipid membrane components. The higher this percentage is, the **quicker** the anesthetic penetrates the membrane.

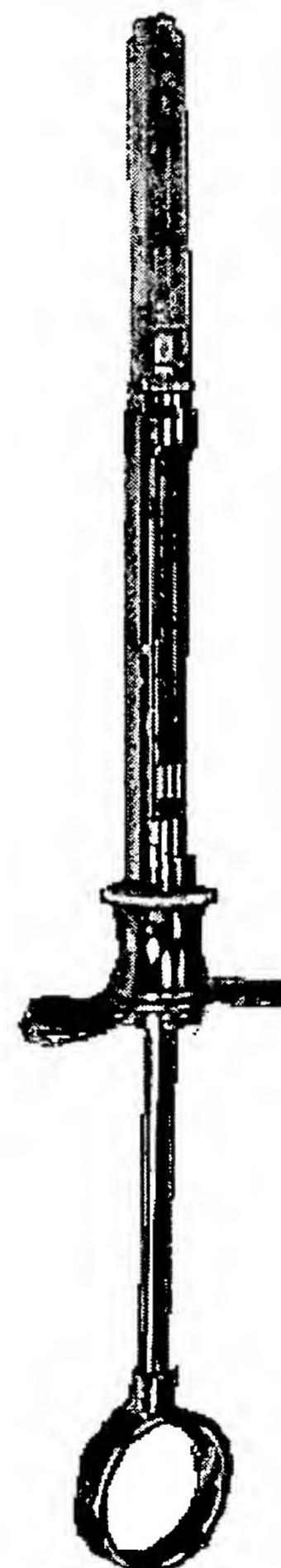
Just because only, say, 18% of an anesthetic solution is available to diffuse through the cell membrane at any one time, this does not mean that all the anesthetic molecules cannot eventually diffuse into the cells. As the number of RN radicals decreases outside of the nerve because of absorption, more of the cationic form (RNH<sup>+</sup>) converts back to the neutral RN form to maintain the dynamic balance between the two forms. The body's PH simply delays the process. Unfortunately, as the time increases, the chances of the unused anesthetic being absorbed into the blood stream also increases, which is why procaine was abandoned soon as lidocaine became available. It simply "wore off" before it had a chance to enter the nerve and take effect.

Once the molecules diffuse through the membrane, the neutral basic RN is once again subject to the PH dependent equation above, and the neutral RN radicals shift back to their cationic form (RNH<sup>+</sup>) to maintain the dynamic balance inside the neuron. **Once inside the nerve the active component that combines with the sodium ion is the acidic cation form (RNH<sup>+</sup>).**

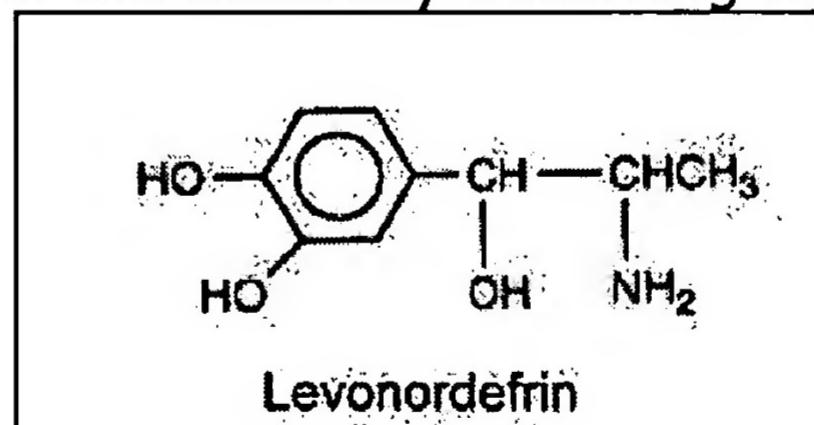
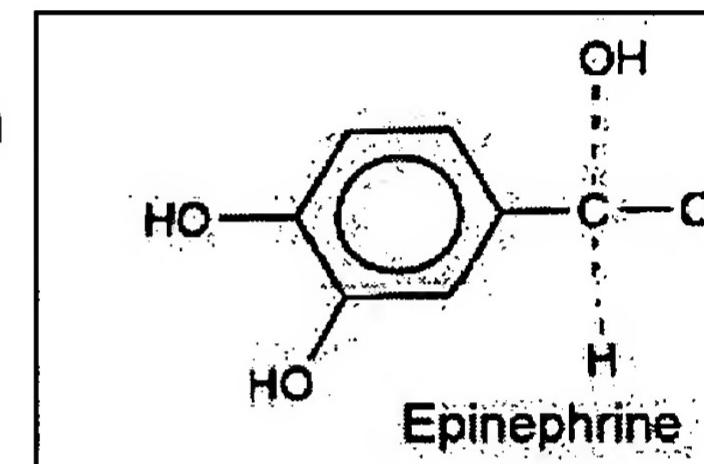
The irony of this situation is that now the slowest diffusing anesthetic

(Bupivacaine with only 18% available to diffuse through the membrane has the distinct advantage of being the **MOST long lasting** anesthetic available, with 82% (100% minus 18%) of the absorbed radicals binding with the sodium channel proteins to block their activity! This doesn't count since it takes so long to diffuse through the nerve membrane that most of it has been reabsorbed by the blood vessels before it ever has a chance to penetrate the nerve membrane.) Bupivacaine (Marcaine®) is used today for prolonged surgical operations as a way of maintaining numbness for many hours after the procedure to help reduce postoperative pain.

## Vasoconstrictors



No matter how quickly an anesthetic agent can enter a nerve, the local blood vessels begin to absorb the unused anesthetic as soon as it is injected. In order to slow this process down, manufacturers of these solutions add a substance that at low concentrations acts to cause the local blood vessels to constrict, or narrow down. This restricts the amount of blood and plasma entering and leaving the site of the injection which has the net effect of slowing the rate of absorption of the anesthetic solution. This keeps the anesthetic solution in place longer and prolongs the action of the drug. The substance used to do this is called a **vasoconstrictor** (vaso refers to blood vessels and constrict means to close down). The vasoconstrictor used in local anesthetic solutions is the naturally occurring hormone **epinephrine** or its analogs called **levonordefrine**.



Epinorepinephrine is an ideal vasoconstrictor because it is manufactured naturally by the body as **adrenaline**, sometimes known as the "fight or flight hormone".

In addition to causing a constriction of blood supply to the area that enters the general circulation it can cause an increase in heart rate and stronger heart beat, along with a feeling of nervousness. These side effects account for the "rush" that some people feel after receiving an anesthetic shot.

### The downside to vasoconstrictors

All anesthetic solutions are sold with added vasoconstrictor. Only

**mepivacaine** and **prilocaine** are sold with or without vasoconstrictor added. Mepivacaine and prilocaine have the advantage of producing only vasodilation and, though both are short acting without their vasoconstrictor added, they still produce adequate anesthesia for procedures. The major advantage of using an anesthetic without vasoconstrictor is that there are virtually no interactions with other medications the patient may be taking. Vasoconstrictors may not be used with types of blood pressure medications, artificial thyroid hormones, tricyclic antidepressants.

Vasoconstrictors are also not used in any body area in which the supply must "double back" on itself. This includes such blind ended appendages as the tip of the nose, or the fingers or toes. In these areas a vasoconstrictor may block all blood flow to the appendage causing tissue necrosis (death of the tissue).

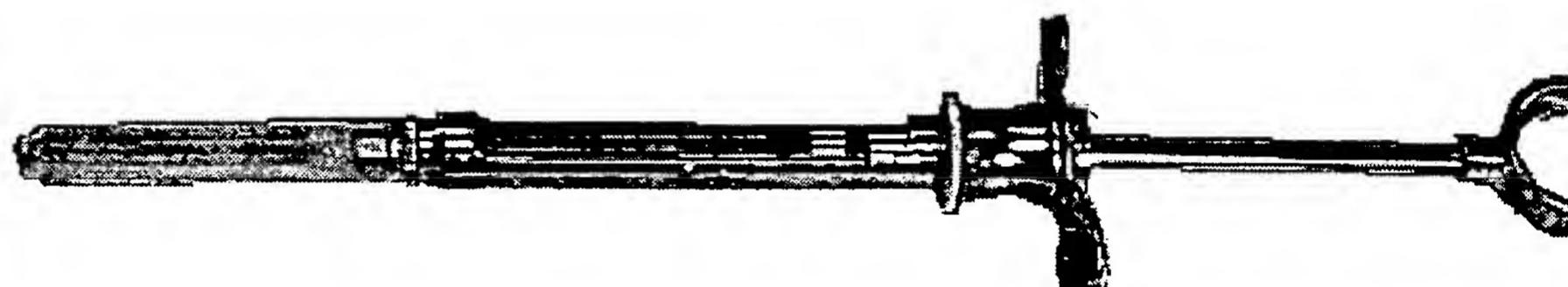
The use of vasoconstrictor does carry one additional penalty for the practitioner. These naturally occurring hormones are not very stable and must be stabilized by the addition of an acidic preservative. The addition of the preservative can lower the PH of the anesthetic solution to a range of 3.8 to 5.0, thus reducing the amount of the neutral basic preservative (RN) and slowing the onset of action of the anesthetic. This effect is thankfully not especially significant, and anesthesia with vasoconstrictor is still far and away the most popular choice among practitioners when clinical considerations permit its use.

## Toxicity; How much is too much?

The maximum dose for local anesthetic solutions is somewhere between 70 mg to 500 mg. Of course, the maximum dose is dependent upon age and health of the patient, the type of solution used, and whether a vasoconstrictor is present or not. These anesthetic agents are distributed in concentrations that are appropriate to their toxicity and their ability to produce anesthesia. All dental anesthetics that are distributed with vasoconstrictor (with the exception of bupivacaine, prilocaine and articaine which will be covered later) come in 2% concentrations. Mepivacaine without vasoconstrictor is distributed in 3% concentration. The carpules (cartridges) that these drugs are distributed in contain 1 ml of solution (Articaine carpules contain 1.7 ml).

Since people vary in age, weight and health, the maximum dose of any given drug that any individual can tolerate varies widely and can only be computed arithmetically. The maximum dose (for a normal adult over 100 pounds and up) for Articaine and lidocaine is 500 mgm. The maximum dose of mepivacaine and etidocaine is 400 mgm. The maximum dose of prilocaine is 600 mgm, and the maximum dose of bupivacaine is 300 mgm. A 2% solution contains 20 mg of anesthetic agent per milliliter with 100 mg per 5 ml.

means that each 1.8 ml cartridge contains 36 mg of agent. In the lidocaine, this works out to about 13 carpules delivered at one time. In children, it works out to about 1/3 to 1/2 that number depending on weight. These doses are **not** considered lethal. They are simply doses at which **some** people **begin** to feel toxic systemic effects from drugs which may include CNS (Central Nervous System) effects (sedation, light headedness, slurred speech, shivering or twitching; rare cases, seizures; or cardiovascular effects such as hypotension (low blood pressure). The incidence of toxicity to local anesthetics in dental setting is extremely rare and generally revolve around very unusual patient centered physiologic abnormalities rather than poor anesthetic technique on the part of the dentist. The most frequently related toxic effect in the dental setting is nervousness and high heart rate, due not to the effect of the anesthetic itself, but rather to the systemic effect of the vasoconstrictor.



### Three special cases

#### **Bupivacaine (Marcaine®)**

Bupivacaine is a special case in dental anesthesia. It is used mostly by surgeons who want to produce very long acting anesthetic effect to delay the post operative pain from their surgery for as long as possible. Bupivacaine comes in 0.5% solution with a vasoconstrictor. It is the most toxic of all the anesthetic agents and this toxicity is reflected in its low concentration in the carpules. As noted in the PKa table above, it has a very alkaline (basic) PKa which means that a relatively large percentage of the uncharged base radical (RN) is available for immediate diffusion through the cell membrane. Thus it takes a fairly long time to be taken up by the cell. However, once inside the cell membrane, over 80% of the molecules that do diffuse become available for binding to the sodium channels and potassium channels. This high protein binding ability causes the drug to remain active for a long time once it has diffused through the cell membrane.

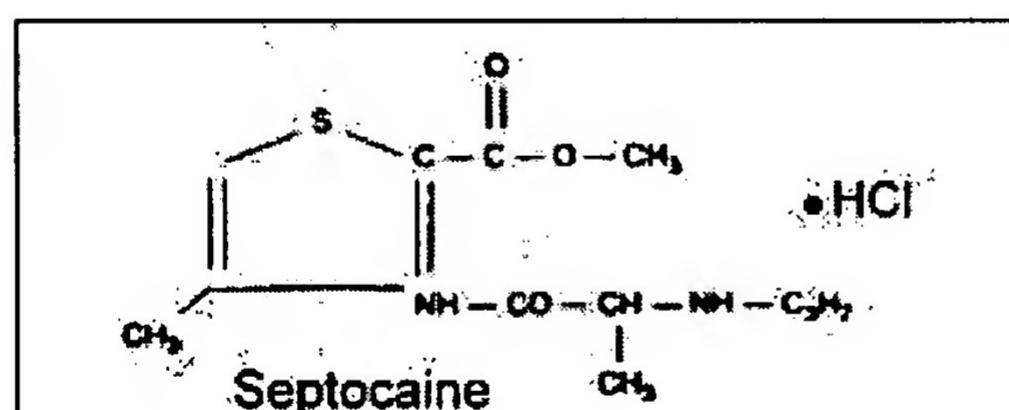
#### **Prilocaine (Citanest®)**

Prilocaine has the same general PKa as lidocaine, which means that for all practical purposes it can be used in the same way and at the same concentrations as lidocaine, producing about the same anesthetic effect in the same amount of time.

setting time for the same duration. It is, however somewhat less toxic in higher doses than lidocaine, and thus is delivered in a 4% solution which places about twice as much molecular anesthetic in proximity to the nerve as is the case with lidocaine or mepivacaine. In addition, since it has little vasodilatory activity, it may be used without a vasoconstrictor. The higher concentration of anesthetic agent, in combination with a vasoconstrictor, therefore, gives this anesthetic the twin advantages of fast onset of activity with prolonged anesthetic activity due to the larger number of molecules available to cross the cell membrane. Unfortunately, the toxicity of a single carpule of 4% prilocaine is still greater than the toxicity of a single carpule of 2% lidocaine which means that fewer carpules can be used before toxic levels are reached.

### Articaine (Septocaine®)

Articaine is the newest addition to the local anesthetic arsenal and was approved by the Food and Drug Administration in April 2000. It has been in use in Europe since 1976 and in Canada since 1983. Its approval in the US has been delayed by the FDA due to the presence of a preservative the agency said was unnecessary in single use carpules and was a potential allergen. It was approved when the French company Sege finally removed the preservative from American shipments.



Articaine has the same PK<sub>a</sub> as Lidocaine, however it is metabolized differently. It has a half life in the body less than 1/4 as long as lidocaine and only 1/5 as long as mepivacaine. This means that

the drug can be injected later in the dental procedure with less likelihood of blood concentrations building to toxic levels. Articaine is formulated in a 4.0% solution with vasoconstrictor. The presence of the vasoconstrictor retards the systemic absorption of the anesthetic allowing higher concentrations of the drug to remain in the area of injection and reduce the absorption into the bloodstream. The higher local concentration of the drug produces a high level of the uncharged radical (RN) to be present at the membrane which brings about very rapid absorption of the drug. In addition, the benzene ring on the left end of the molecule has been replaced with a thiophene ring. This modification allows for faster and more complete absorption through the nerve cell membrane. The ability of this drug to penetrate barriers is so great that it has been shown to penetrate thick bone to produce anesthesia in a way that other local anesthetics cannot. Articaine has become the local anesthetic of choice for dental procedures.